BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12410

Optimal sampling of antipsychotic medicines: a pharmacometric approach for clinical practice

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Keywords
antipsychotic medicines, optimal sampling, pharmacometrics, population pharmacokinetics, therapeutic drug monitoring

Received
23 January 2014

Accepted
19 April 2014

Accepted Article Published Online
29 April 2014

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Antipsychotic medicines are widely prescribed for the management of schizophrenia. However there are high rates of discontinuation, drug switching and dose adjustment which in part is due to the large inter-individual variability in response to these medicines.
- Pharmacometric approaches to determine pharmacokinetic parameters using sparse sampling strategies are increasing. However the optimal sampling time points which determine the precision and accuracy of these parameters are typically not taken into account.
- Aside from clozapine, therapeutic drug monitoring strategies for other antipsychotic medicines are not implemented in hospital settings routinely and this is in part due to the lack of clearly defined exposure–response relationships.

WHAT THIS STUDY ADDS

- This analysis has utilized pharmacometric tools to provide optimal sampling time points for future population PK/PD studies, guidance for therapeutic drug monitoring and to allow clinicians practical solutions to calculate complex pharmacokinetic parameters when interpreting exposure to antipsychotic medicines.
- Bayesian population PK estimates using sparse but optimal time points yield excellent correlations and only small errors when compared with extensive sampling strategies.
- Trough concentrations only provide modest correlations to exposure of antipsychotic drugs except in the case of clozapine, where there is an excellent correlation, and this may relate to difficulties establishing exposure–response relationships of other antipsychotic medicines.

AIM

To determine optimal sampling strategies to allow the calculation of clinical pharmacokinetic parameters for selected antipsychotic medicines using a pharmacometric approach.

METHODS

This study utilized previous population pharmacokinetic parameters of the antipsychotic medicines aripiprazole, clozapine, olanzapine, perphenazine, quetiapine, risperidone (including 9-OH risperidone) and ziprasidone. D-optimality was utilized to identify time points which accurately predicted the pharmacokinetic parameters (and expected error) of each drug at steady-state. A standard two stage population approach (STS) with MAP-Bayesian estimation was used to compare area under the concentration–time curves (AUC) generated from sparse optimal time points and rich extensive data. Monte Carlo Simulation (MCS) was used to simulate 1000 patients with population variability in pharmacokinetic parameters. Forward stepwise regression analysis was used to determine the most predictive time points of the AUC for each drug at steady-state.

RESULTS

Three optimal sampling times were identified for each antipsychotic medicine. For aripiprazole, clozapine, olanzapine, perphenazine, risperidone, 9-OH risperidone, quetiapine and ziprasidone the CV% of the apparent clearance using optimal sampling strategies were 19.5, 8.6, 9.5, 13.5, 12.9, 10.0, 16.0 and 10.7, respectively. Using the MCS and linear regression approach to predict AUC, the recommended sampling windows were 16.5–17.5 h, 10–11 h, 23–24 h, 19–20 h, 16.5–17.5 h, 22.5–23.5 h, 5–6 h and 5.5–6.5 h, respectively.

CONCLUSION

This analysis provides important sampling information for future population pharmacokinetic studies and clinical studies investigating the pharmacokinetics of antipsychotic medicines.

Introduction

Antipsychotic medicines are utilized widely in the management of mental health disorders, including schizophrenia, schizoaffective disorder, bipolar disorder and major depression [1, 2]. However, The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), the largest randomized controlled trial investigating antipsychotic therapy in patients with schizophrenia, found that 74% of patients discontinued the study medicine before 18 months due to lack of efficacy and/or intolerable side effects [3]. There are several factors that are important in the discontinuation of antipsychotic medicines among patients with schizophrenia, but medication efficacy is a key component [4–8]. The wide variability in the pharmacokinetics of these drugs, which often results in significant differences in pharmacodynamics, is considered to be a key contributor to medication efficacy [9, 10]. Therefore, there is increasing interest in pharmacometric approaches such as population pharmacokinetic/pharmacodynamic (PK/PD) studies for quantifying patient variability in response to antipsychotic medicines [3, 11, 12].

Population pharmacokinetics is a useful approach to identify covariates (e.g. age, gender, genetic polymorphisms) that have a significant impact on drug disposition [13, 14]. An advantage of the population approach over traditional pharmacokinetic analysis is that sparse, rather than rich data can be used to obtain accurate estimates of PK/PD model parameters. However, the precision and accuracy of these parameters is dependent on the time of sample collection amongst a number of other factors [15–19]. D-optimality (optimal sampling) is an underutilized pharmacometric tool that identifies the optimal blood sampling times that maximize the precision and accuracy of the pharmacokinetic or pharmacodynamic parameters to be estimated [20–22]. Importantly, optimal sampling has been utilized to design effective population pharmacokinetic studies in a number of disease areas, including infectious disease, oncology and paediatrics [23–28]. However, there are no studies reporting optimal sampling strategies for future population PK/PD studies with antipsychotics.

Pharmacokinetic studies with optimized sampling times provide insights that can improve therapeutic drug monitoring (TDM), which, however, remains a controversial topic for antipsychotic medicines [29]. TDM is recommended for clozapine, due largely to its potentially fatal toxicities, whereas for most others it has limited clinical uptake [30]. The basis of TDM is to identify a plasma or blood drug concentration window, typically based on a single trough concentration, which is reflective of actual drug exposure and ultimately, drug response. The gold standard for measurement of exposure to a drug is the area under the blood or plasma concentration–time curve (AUC), but this usually requires extensive blood sampling to quantify accurately. Therefore, generating population estimates of AUC using a sparse number of blood samples can be of great value because one can more efficiently correlate drug exposure with drug effects.

The aim of this study was to determine optimal sampling strategies to estimate the pharmacokinetic parameters of antipsychotic medicines using pharmacometric approaches. In addition, we propose algorithms and sampling windows to calculate rapidly AUCs for antipsychotics that may be useful to clinicians for monitoring patient compliance and to enhance the value of TDM of antipsychotics or changes in drug exposure with time.

Methods

Study design

Population parameter estimates of clearance, volume of distribution and absorption rates of several antipsychotic medications commonly used in ambulatory patients with schizophrenia or schizoaffective disorder were extracted from published studies in order to conduct the blood sampling optimization analyses. The strategy used, population pharmacokinetic studies accessed and the population models we utilized to analyze the respective data are presented in Supplementary Figure S1 and Supplementary Table S1 [3, 31–48].

Data selection

The CATIE trials developed population PK models of the antipsychotic medicines olanzapine, perphenazine, quetiapine, risperidone and ziprasidone in the largest cohort of patients with schizophrenia enrolled in a randomized trial to date [3]. Therefore, to reduce variability between studies in modelling strategy and patient selection for optimal sampling, the PK models and parameters from the CATIE data were used when possible. For aripiprazole and clozapine, separate population PK modelling studies were used [35, 38]. Only one published abstract was available for the population PK of paliperidone, but it was excluded from the analysis due to the complexity of the model [43]. Table 1 outlines the pharmacokinetic parameters extracted and used for our analyses. As the CATIE data for each antipsychotic drug has been analyzed previously to produce pharmacokinetic models and published in several manuscripts, we selected the most recently published study [3, 31, 33, 35, 37, 38, 48]. Typically, different doses were prescribed to subjects within a study, and therefore the dose we selected in the current analysis was the median prescribed dose. This is not anticipated to impact on the pharmacokinetic values chosen as these drugs display linear pharmacokinetics in the range of typically prescribed dose range.

Table 1

Pharmacokinetic parameters of atypical antipsychotic medicines and inter-individual variability (IIV) based on population studies

Parameter	Aripiprazole	Clozapine†	Olanzapine	Perphenazine	Risperidone and 9-OH risperidone†	Quetiapine	Ziprasidone
Dose (mg)	30	200	20	25	5	400	80
Dosing Interval (h)	24	12	24	24	24	12	12
CL/*F* (apparent clearance) (l h^{-1}) (IIV)	2.37 (30.5)	36.7 (44.5)	26.1 (68.0)	483 (50.0)*	65.4 (56.6) & 8.83	104 (78.0)	122 (64.8)
V/*F* (apparent volume of distribution) (l) (IIV)	192 (31.6)	950 (50.0)*	2150 (86.0)	18200 (50.0)*	444 (36.1) (for both)	653 (100.0)	1060 (104.4)
k_a (absorption rate constant) (h^{-1}) (IIV)	1.06 (Fixed)	0.8 (fixed)	0.5 (fixed)	1.6 (fixed)	1.7 (fixed) & (kf) = 0.595 (metabolite fraction)	2.0 (141.0)	0.5 (Fixed)
$t_{1/2}$ (half-life) (h)	56.2	17.9	33	9.5	8.5	7.0	7.0
SD1slope (proportional residual error)	0.15	0.15	0.15	0.15	0.15	0.15	0.15
SD1int (additive residual error)	0.0001	0.025	0.00025	0.0001	0.0001	0.025	0.0005
Reference	(Kim *et al.*) [38]	(Ismail *et al.*) [35]	(Bigos *et al.*) [31]	(Jin *et al.*) [37]	(Feng *et al.*) [70]	(Bigos *et al.*) [3]	(Wessels *et al.*) [48]

*Fixed at 50.0% no IIV data given or fixed in study. †Extensive *CYP2D6* metabolizers utilized for this data.

Population pharmacokinetic models

The population PK models were all one compartment models with first order absorption and elimination as depicted in Supplementary Figure S2. Risperidone and its major active metabolite 9-OH risperidone were modelled as separate one compartment pharmacokinetic models utilizing data from extensive CYP2D6 metabolizers only. Three pharmacokinetic parameters estimated in each analysis were apparent clearance (CL/*F*), the apparent volume of distribution (*V*/*F*) and the absorption rate constant (k_a). Notable changes were made to the population parameters described by some previous studies, specifically in the residual error models and covariance-variance between CL/*F* and *V*/*F*. The residual error model describes differences between observed and model predicted values after accounting for the inter-individual variability. Whereas some studies indicated a proportional error or additive error model, in the current analysis, all drugs were assigned mixed error models including both additive and proportional components ((*Y*): $\sigma = SD_{slope}\ Y + SD_{intercept}$) in which SD_{slope} and $SD_{intercept}$ are the variance parameters. The additive error was set as the lower limit of drug concentration quantification of each antipsychotic medicine based on the drug assay recorded in the publication. The proportional error was set at 0.15 (15% coefficient of variation) for all antipsychotic medicines assuming that this would be the expected, unexplained error in a well-controlled clinical study investigating the pharmacokinetics of antipsychotic medicines. The simulations included inter-individual variability (CV%) in CL/*F* and *V*/*F* and when unavailable, an estimate of 50% was assumed. In order to maintain realistic concentrations and PK parameters the covariance-variance of the apparent clearance (CL/*F*) and volume of distribution (*V*/*F*) was included for the simulations and population analysis. When covariance-variance values for CL/*F* and *V*/*F* were not available, a modest correlation of 0.2 was assumed.

Optimal sampling (D-optimality)

Optimal sampling times were determined using the SAMPLE Module of the ADAPT 5 software program (Biomedical Simulations Resource, University of Southern California) based on the D-optimality criterion (minimization of parameter uncertainty). The theoretical basis of D-optimality based optimal sampling has been described previously in detail [49]. As explained by Jamsen *et al*., an optimal design (i.e. set of blood concentration sampling times) for a population pharmacokinetic model is the design that which will maximize the determinant of the population Fisher information matrix, thereby minimizing the standard errors (i.e. maximizing the precision) of the parameter estimates [25]. The optimal sampling times selected were based on the drug concentrations from the dose interval once steady-state for the drug had been reached (verified by visual inspection).

To conduct the optimal sampling analysis for each drug, 0.5 h sampling time intervals within the respective dosing interval of each drug were optimized. As one compartment models were employed for all drugs, each model consisted of three parameters (CL/*F*, *V*/*F*, k_a) and therefore three sampling time points were detected that were optimal for estimating each of these parameters respectively. To ensure the 'optimal' times were selected and to test the sensitivity of these, the times were varied and re-tested to assess the bias (CV%) and the D-optimality criterion was compared. These time points consisted of intervals at 0.5 h prior to the optimally selected times.

Monte Carlo simulations

Monte Carlo simulation (MCS) incorporating prior defined inter-individual variability and residual error was implemented using the SIM option with population error in ADAPT V. In order to have reasonable power and variability, 1000 patients were simulated at 0.5 h time points to steady-state. Previous studies have indicated that

steady-state drug concentrations can be assumed to be the drivers of the exposure–response relationship [50]. In order to calculate the 'true' AUC, this was incorporated as a secondary parameter based on numerical integration within ADAPT.

Standard two stage with MAP-Bayesian estimation

Population analysis using the standard two stage (STS) option and maximum *a posteriori* Bayesian (MAP) was used in ADAPT V. The initial extensive sampling time points (every 0.5 h) were replaced by the optimal sampling time points identified using D-optimality. The AUC(0,τ) was calculated for each individual based on the optimal sampling strategy and compared with the AUC(0,τ) obtained from extensive sampling analysis in order to calculate the CV% error.

Proposed sampling algorithms

The AUC(0,τ) obtained from each participant in the MCS was used as a dependent variable in a forward stepwise linear regression analysis where each 0.5 h time point was used as an independent variable. The CV% was reported as: {(True AUC(0,τ) – estimated AUC(0,τ))/True AUC(0,τ)}*100. Based on the regression analysis, a concentration–time algorithm which relates the most predictive time–concentration data points to the 'true AUC(0,τ)' was conducted for the four best sampling time points for each drug. The algorithm for the trough concentration was also presented. Selection of the best sampling strategy was based on consideration of the correlation coefficient (r^2) and the reduction in the CV%. An additional time point was deemed as significantly improving the sampling strategy if it resulted in an increase in the r^2 of 0.02 and/or decrease in the CV% of 5.

Selection of 'sampling windows'

The recommended hourly sampling window was built on the MCS used to determine the proposed sampling algorithms by identifying the best consecutive combination of three time points (each separated by at least 0.5 h interval), which determined the AUC(0,τ). The best subsets approach was used in linear regression to identify this and was based on assessment of the strongest correlation and lowest CV% for each concentration–time point.

Statistical methods

The AUC was determined based on numerical integration techniques in ADAPT V. Forward stepwise regression analysis was used to assess the most predictive time points of the AUC(0,τ). The best subsets approach using linear regression analysis was used to identify the most important sampling window based on correlation of each concentration time point to AUC(0,τ). Pearson's correlation coefficient (r^2) was used to assess the strength of relationships between variables. SYSTAT v13.0 was used to calculate mean, standard deviations, 95% confidence intervals and precision as a CV% of the pharmacokinetic parameters. Calculation of absolute bias was based on the methods recommended by Sheiner & Beal, i.e. the sum of the root mean square of the error $\sqrt{(\text{predicted} - \text{true})^2}$ divided by the number of subjects [51]. R statistical program was used to structure data files for standard two stage population analysis. Microsoft Excel 2013 was used to create graphics.

Results

Antipsychotic medicines

Table 1 outlines the dose, dosing interval and pharmacokinetic parameters utilized in the optimal sampling analysis [3, 31, 33, 35, 37, 38, 48]. The standard dose ranges and regimens for each drug were quite different. Aripiprazole, olanzapine, perphenazine and risperidone are prescribed at relatively low doses daily. The dosing ranges for clozapine, quetiapine and ziprasidone are higher and they are dosed twice daily. Variability in the pharmacokinetics of the seven antipsychotic medicines was also large. The k_a, which was typically fixed in most population studies ranged from 0.5 h^{-1} (olanzapine and ziprasidone) to 2.0 h^{-1} (quetiapine), a 4-fold variation. The V_d/F ranged from 444 l (risperidone) to 18200 l (perphenazine), a 40-fold variation, while the CL/*F* ranged from 2.37 l h^{-1} (aripiprazole) to 483 l h^{-1} (perphenazine), a 200-fold variation.

Optimal sampling

The pharmacokinetic models analyzed were all one compartment models with three pharmacokinetic parameters (CL/*F*, *V*/*F* and k_a). The time points selected by optimal sampling analysis are shown in Table 2 and Figure 1. For all drugs, a time point was selected in the absorption phase, distribution/metabolism phase and elimination phase, respectively. The range of the time point in the absorption phase was 0.2–1.1 h, for distribution/metabolism the range in time points was 1.0–8.4 h and in the elimination phase the range of the time points was 12.0–24.0 h post-dose. Table 2 shows the pharmacokinetic parameter values and the CV% (expected error) associated with each parameter based on the selected sampling time points. The lowest CV% for the CL/*F* based on the optimal sampling time points identified was, in order, clozapine (8.6%), olanzapine (9.5%), 9-OH risperidone (10.0%), ziprasidone (10.7%), risperidone (12.9%), perphenazine (13.5%), quetiapine (16.0%) and aripiprazole (19.5%). The CV%s for the *V*/*F* and k_a were relatively high for all antipsychotic medicines due to the nature of the study design (i.e. sampling at steady-state and the sparse optimal sampling strategy). The second sampling strategy chosen to indicate

Table 2

Optimal sampling time points, and secondary sampling set (italicized), of atypical antipsychotic medicines and the expected error on pharmacokinetic parameters based on defined sampling time points during steady-state dosing interval

Drug	Optimal sampling time points (time after dose in h)	Pharmacokinetic parameters and expected standard error CL/*F* (l h^{-1}) (CV%)	*V*/*F* (l) (CV%)	k_a (h^{-1}) (CV%)	$t_{1/2}$ (h) (CV%)
Aripiprazole	0.9; 3.9; (trough 23–24) *0.5; 3.5; 23.5*	2.37 *(19.50)* *(21.0)*	192.0 *(178.5)* *(173.2)*	1.06 *(354.2)* *(433.1)*	56.15 (181.5) *(174.3)*
Clozapine	1.1; 4.6; (trough 11–12) *0.5; 4.0; 11.5*	36.7 *(8.64)* *(8.78)*	950.0 *(85.93)* *(81.63)*	0.80 *(136.7)* *(164.0)*	17.94 *(83.59)* *(78.71)*
Olanzapine	1.7; 8.4; (trough 23–24) *1.0; 8.0; 23.5*	26.1 *(9.45)* *(9.20)*	2150.0 *(86.82)* *(86.08)*	0.50 *(164.6)* *(174.2)*	59.14 *(93.29)* *(92.24)*
Perphenazine	0.5; 3.5; (trough 23–24) *0; 3.0; 23.5*	483.0 *(13.46)* *(13.45)*	18200 *(56.02)* *(54.03)*	1.60 *(117.9)* *(257.9)*	26.12 *(53.06)* *(50.02)*
Risperidone	0.2; 1; 18.4 *0; 0.5; 18.0*	65.4 *(12.92)* *(44.41)*	444.0 *(19.48)* *(72.92)*	1.7 *(31.26)* *(93.65)*	4.70 *(14.13)* *(31.07)*
9-OH risperidone	1.5; 7.5; (trough 23–24) *1.0; 7.0; 23.5*	8.83 *(9.95)* *(10.0)*	444.0 *(75.01)* *(75.11)*	0.595 *(136.9)* *(137.9)*	34.85 *(71.82)* *(71.84)*
Quetiapine	0.3; 2.4; (trough 11–12) *0; 2.0; 11.5*	104.0 *(15.97)* *(16.24)*	653.0 *(31.33)* *(30.77)*	2.00 *(55.43)* *(73.39)*	4.35 (27.95) *(26.43)*
Ziprasidone	1.1; 5.9; (trough 11–12) *0.5; 5.5; 11.5*	122.0 *(10.69)* *(13.24)*	1060.0 *(65.01)* *(64.11)*	0.50 *(88.74)* *(89.32)*	6.02 (59.03) *(58.83)*

the sensitivity of the optimal times is shown in Table 2. Figure 1 shows a visual representation of the optimal sampling times selected following attainment of steady-state for each antipsychotic medicine.

Monte Carlo simulation and population analysis with MAP-Bayesian estimation

MCS was used to simulate 1000 subjects at 0.5 h time points with inter-individual variability and population error for each antipsychotic medication. The minimum and maximum ranges of the apparent clearance for aripiprazole (2.12–5.27 l h^{-1}), clozapine (6.47–223.91 l h^{-1}), olanzapine (2.29–117.96 l h^{-1}), perphenazine (112.21–2298.49 l h^{-1}), quetiapine (80.16–142.34 l h^{-1}), risperidone (50.0–90.29 l h^{-1}), 9-OH risperidone (4.22–20.59 l h^{-1}) and ziprasidone (18.90–832.10 l h^{-1}) were comparable with previous studies, indicating that simulation accurately reflected previous population analysis. Using the same subjects generated from the MCS, a STS population analysis with MAP-Bayesian estimation was conducted using the three sampling times identified by optimal sampling. Table 3 shows the MAP-Bayesian predicted AUC(0,τ), expected CV%, correlation (r^2), bias and precision of the prediction generated from the extensive sampling. Overall, the optimal sampling strategies using the population STS with MAP-Bayesian estimation performed very well with CV% of the AUC(0,τ) ranging from 1.30% (perphenazine) to 15.65% (quetiapine). Similarly, the correlation between the 'true' AUC(0,τ) and optimal sampling AUC(0,τ) was excellent for most antipsychotic medicines with a range of 0.80 (aripiprazole) to 1.00 (perphenazine) with the exception of risperidone ($r^2 = 0.55$).

Proposed sampling algorithms

The subjects generated from MCS were utilized to identify concentration–time algorithms using a biostatistics approach to predict AUC(0,τ) for each antipsychotic medicine. Table 4 shows the forward stepwise linear regression results for the most predictive time points taking into account one, two, three, four and trough sampling strategies where concentrations at the selected time points are related to AUC(0,τ) numerically. The AUC(0. τ), r^2, precision (CV%) and the bias (absolute value of the AUC(0,τ)) are shown. The average AUC(0,τ) of the simulated subjects for aripiprazole, clozapine, olanzapine, perphenazine, risperidone, 9-OH risperidone, quetiapine and ziprasidone was 9.46 μg ml^{-1} h, 7.22 μg ml^{-1} h, 1.09 μg ml^{-1} h, 63.0 μg l^{-1} h, 77.0 μg l^{-1} h, 0.60 μg ml^{-1} h, 4.91 μg ml^{-1} h and 0.90 μg ml^{-1} h, respectively. The best sampling strategy was based on consideration of the CV%, bias and Pearson's correlation (r^2) as described in the methods. For aripiprazole, a four sampling time point strategy was recommended (2.16 + 5.13*(20 h) + 5.10*(17 h) + 5.05*(21 h) + 4.73*(19.5 h)) (CV% of 4.9, bias of 0.46 and r^2 of 0.90), for clozapine, a two sampling strategy (1.10 + 6.19*(10 h) + 5.56*(11.5 h)) (CV% of 10.0, bias of 0.79 and r^2 of 0.97), for olanzapine, a three sampling strategy (–0.060 + 8.94*(16 h) + 11.61*(20h) + 10.86*(23 h)) (CV% of 13.3, bias of 0.07 and r^2 of 0.86), for perphenazine, a three sampling strategy (0.006 + 9.06*(20 h) + 6.75*(5 h) + 7.76*(17.5 h)) (CV% of 8.7, bias of 0.005 and r^2 of 0.93), for quetiapine, a four sampling strategy (0.486 + 3.27*(6h) + 2.20*(3.5 h) + 3.53*(6.5 h) + 1.43*(0.5 h)) (CV% of 6.3, bias of 0.49 and r^2 of 0.94), for risperidone, a four sampling strategy (0.048 + 6.26*(17 h) + 5.00*(15 h) + 4.09*(13 h) + 3.02*(11 h)) (CV%

Table 3

MAP-Bayesian estimation to predict AUC with optimal sampling time points

Optimal sampling time points (h)	Population analysis AUC (μg l^{-1} h)	CV%	Correlation (r^2)
Aripiprazole			
(True average AUC(0,τ) = 9.46 ± 1.31)			
Optimal sampling time points (0.9, 3.9, 24)	9.48	6.70	0.80
Clozapine			
(True average AUC(0,τ) = 14.72 ± 8.51)			
Optimal sampling time points (1.1, 4.6, 12)	14.75 ± 8.27	8.67	0.98
Olanzapine			
(True average AUC(0,τ) = 1.09 ± 0.71)			
Optimal sampling time points (1.7, 8.4, 24)	1.02 ± 0.59	11.90	0.90
Perphenazine			
(True average AUC(0,τ) = 0.063 ± 0.031)			
Optimal sampling time points (0.5, 3.5, 24)	0.063 ± 0.029	1.30	1.00
Risperidone			
(True average AUC(0,τ) = 0.077 ± 0.006)			
Optimal sampling time points (0.2,1,18.4)	0.077 ± 0.006	6.40	0.55
9-OH risperidone			
(True average AUC(0,τ) = 0.597 ± 0.145)			
Optimal sampling time points (1.5,7.5, 24)	0.599 ± 0.139	6.90	0.92
Quetiapine			
(True average AUC(0,τ) = 4.91 ± 2.21)			
Optimal sampling time points (0.3,2.4,12)	5.05 ± 2.28	15.65	0.93
Ziprasidone			
(True average AUC(0,τ) = 0.90 ± 0.56)			
Optimal sampling time points (1.1, 5.9, 12)	0.91 ± 0.57	8.56	0.98

of 4.1, bias of 0.003 and r^2 of 0.75), for 9-OH risperidone, a three sampling strategy (0.113 + 7.63*(20 h) + 7.86*23.5 h) + 7.04*(19 h)) (CV% of 5.8, bias of 0.034 and r^2 of 0.91) and for ziprasidone, a two sampling strategy (7.31*(6 h) + 3.75*(0.5 h)) (CV% of 8.3, bias of 0.09 and r^2 of 0.95). The strongest correlation between trough concentration time point and AUC(0,τ) was shown for clozapine ($r^2 = 0.93$, bias of 1.09 and CV% of 13.0) and olanzapine ($r^2 = 0.79$, bias of 0.30 and CV% of 17.2). The weakest correlation between trough concentration time point and AUC(0,τ) was for quetiapine ($r^2 = 0.63$, bias of 2.72 and CV% of 41.2). The algorithms generated (i.e. the concentration–time algorithm to predict AUC) allow for rapid calculation of the AUC after obtaining drug concentration at various times specified.

Identification of sampling windows

Figure 2 depicts the hourly sampling windows for each antipsychotic drug; aripiprazole (16.5–17.5 h), clozapine (10–11 h), olanzapine (23–24 h), perphenazine (19–20 h), risperidone (16.5–17.5 h), 9-OH risperidone (22.5–23.5 h), quetiapine (5–6 h) and ziprasidone (5.5–6.5 h). The correlation coefficients (r^2) for the best subset of consecutive time points for the prediction of AUC are displayed in Figure 2: aripiprazole (0.51, 0.45, 0.48), clozapine (0.90, 0.90, 0.86), olanzapine (0.72, 0.72, 0.71), perphenazine (0.81, 0.81, 0.81), risperidone (0.43, 0.46, 0.41), 9-OH risperidone (0.74, 0.74, 0.76), quetiapine (0.77, 0.77, 0.79) and ziprasidone (0.90, 0.91, 0.90).

Discussion

The clinical use of antipsychotic medicines is often very difficult given the wide variability in their PK/PD, the large choice of potentially efficacious medicines available and the challenging patients in which they are used. Newer and more sophisticated approaches to drug and dose selection and/or dose adjustment are urgently needed to improve antipsychotic efficacy and clinical outcomes [52, 53]. Pharmacometric tools have been utilized in this analysis to inform the study design of future population pharmacokinetic studies investigating currently used antipsychotic medicines, and also to provide clinicians with guidance regarding TDM strategies that can be implemented in clinical situations. The results demonstrate that there is wide variability in the optimal blood concentration sampling strategies for commonly prescribed antipsychotic medicines due to their diverse pharmacokinetic profiles. This finding has broad implications for TDM, as well as drug and dose selection.

Previous studies investigating population PK/PD of antipsychotic medicines have typically used sparse sampling, but the effectiveness of the sampling schedules of these studies has not been evaluated [3, 31, 33, 35–38, 46–48, 50, 54–56]. The current study recommends the collection of samples at three time points for optimal sampling of each antipsychotic medicine. This strategy delivers the most reliable estimates of CL/*F*, *V*/*F* and k_a, the three parameters derived from the one compartment models utilized in the analysis [20]. The CL/*F* parameter is well estimated using the optimal sampling strategies chosen, with CV% between 10% and 20% for all antipsychotic drugs evaluated. Aside from risperidone and quetiapine, the *V*/*F* and k_a were not well estimated based on the optimal sampling strategies presented and this is most likely due to the study design and administration route, i.e. these parameters are best estimated following the first dose of a drug rather than at steady-state. The sensitivity analysis of the optimal sampling time-points, based on 0.5 h time points prior to the selected optimal time points, indicates that although the CL parameter estimated using optimal sampling strategy provides good estimates for CL, for perphenazine and olanzapine the second sampling strategy performed better. However, there was much greater error in the parameter for k_a. This

Table 4

Identification and evaluation of predictive time points of the AUC for each drug

Drug	Single time point	Two time points	Three time points	Four time points	Trough time point only
Aripiprazole					
True mean of simulated AUC(0, τ) = 9.46 ± 1.31					
Correlation (r^2)	0.71	0.82	0.87	0.90	0.67
Precision (CV% of AUC)	7.8	6.2	5.5	4.9	8.1
Absolute bias (μg ml^{-1} h)	0.73	0.59	0.51	0.46	0.76
(95% CI)	*(0.69, 0.76)*	*(0.56, 0.61)*	*(0.49, 0.54)*	*(0.44, 0.48)*	*(0.73, 0.80)*
Concentration–time algorithms to predict AUC	4.92 + 12.53 (20 h)	3.43 + 8.37 (20 h) + 8.01 (17 h)	2.74 + 6.33 (20 h) + 6.23 (17 h) + 5.85 (21 h)	2.16 + 5.13 (20 h) + 5.10 (17 h) + 5.05 (21 h) + 4.73 (19.5 h)	5.34 + 11.95 (24 h)
Clozapine					
True mean of simulated AUC0-tau = 7.22 ± 4.17					
Correlation	0.95	0.97	0.98	0.98	0.93
Precision (CV% of AUC)	13.0	10.0	9.0	8.0	13.0
Absolute bias (μg ml^{-1} h^{-1})	1.00	0.79	0.68	0.61	1.09
(95% CI)	*(0.94, 1.05)*	*(0.75, 0.83)*	*(0.64, 0.71)*	*(0.57, 0.64)*	*(1.02, 1.15)*
Concentration–time algorithms to predict AUC	1.33 + 11.02 (10 h)	1.10 + 6.19 (10 h) + 5.56 (11.5 h)	1.06 + 4.29 (10 h) + 3.61 (11.5 h) + 3.85 (10.5 h)	0.92 + 3.34 (10 h) + 3.33 (11.5 h) + 3.33 (10.5 h) + 2.61 (9.5 h)	1.61 + 11.24 (12 h)
Olanzapine					
True mean of simulated AUC(0, τ) = 1.09 ± 0.71					
Correlation (r^2)	0.82	0.85	0.86	0.86	0.79
Precision (CV% of AUC)	16.0	14.1	13.3	13.0	17.2
Absolute bias (μg ml^{-1} h^{-1})	0.18	0.09	0.07	0.07	0.30
(95% CI)	*(0.167, 0.182)*	*(0.088, 0.098)*	*(0.064, 0.071)*	*(0.062, 0.069)*	
Concentration–time algorithms to predict AUC	0.007 + 29.54 (20 h)	–0.021 + 16.47 (20 h) + 14.44 (23 h)	–0.060 + 8.94 (16 h) + 11.61 (20 h) – 10.86 (23 h)	–0.059 + 6.86 (16 h) + 9.66 (20 h) – 8.73 (23 h) + 6.52 (24 h)	0.065 + 29.66 (24 h)
Perphenazine					
True mean of simulated $AUC_{0\text{-}tau}$ = 0.063 ± 0.031					
Correlation (r^2)	0.82	0.90	0.93	0.95	0.77
Precision (CV% of AUC)	15.2	10.6	8.7	7.4	17.1
Absolute bias (μg ml^{-1} h^{-1})	0.009	0.006	0.005	0.005	0.010
(95% CI)	*(0.008, 0.009)*	*(0.006, 0.007)*	*(0.005, 0.005)*	*(0.004, 0.005)*	*(0.010, 0.011)*
Concentration–time algorithms to predict AUC	0.02 + 20.84 (20 h)	0.006 + 13.89 (20 h) + 8.92 (5 h)	0.006 + 9.06 (20 h) 6.75 (5 h) 7.76 (17.5 h)	0.004 + 6.80 (20 h) + 5.32 (5 h) 5.60 (17.5 h) 5.99 (13 h)	0.024 + 21.09 (24 h)
Risperidone					
True mean of simulated AUC(0, τ) = 0.077 ± 0.007					
Correlation (r^2)	0.46	0.61	0.70	0.75	0.71
Precision (CV% of AUC)	5.7	4.9	4.5	4.1	6.0
Absolute bias (μg ml^{-1} h^{-1})	0.004	0.003	0.003	0.003	0.005
(95% CI)	*(0.004, 0.004)*	*(0.003, 0.004)*	*(0.003, 0.003)*	*(0.003, 0.003)*	*(0.004, 0.005)*
Concentration–time algorithms to predict AUC	0.063 + 13.47 (17 h)	0.057 + 9.40 (17 h) + 7.24 (15 h)	0.052 + 7.45 (17 h) + 5.92 (15 h) + 4.66 (13 h)	0.048 + 6.26 (17 h) + 5.00 (15 h) + 4.09 (13 h) + 3.02 (11 h)	0.070 + 18.97 (24 h)
9-OH risperidone					
True mean of simulated AUC(0, τ) = 0.597 ± 0.145					
Correlation (r^2)	0.77	0.87	0.91	0.93	0.74
Precision (CV% of AUC)	9.3	6.8	5.8	4.9	10.1
Absolute bias (μg ml^{-1} h^{-1})	0.055	0.041	0.034	0.029	0.057
(95% CI)	*(0.052, 0.057)*	*(0.039, 0.043)*	*(0.032, 0.036)*	*(0.028, 0.031)*	*(0.054, 0.060)*
Concentration–time algorithms to predict AUC	0.190 + 18.59 (20 h)	0.141 + 10.81 (20 h) + 10.68 (23.5 h)	0.113 + 7.63 (20 h) + 7.86 (23.5 h) + 7.04 (19 h)	0.105 + 5.75 (20 h) + 6.11 (23.5 h) + 5.70 (19 h) + 5.58 (23 h)	0.218 + 18.84 (24 h)

Table 4
Continued

Drug	Single time point	Two time points	Three time points	Four time points	Trough time point only
Quetiapine					
True mean of simulated AUC(0,τ) = 4.91 ± 2.21					
Correlation (r^2)	0.79	0.88	0.91	0.94	0.63
Precision (CV% of AUC)	29.7	14.4	13.1	6.3	58.7
Absolute bias (μg ml^{-1} h^{-1})	1.437	0.809	0.705	0.486	2.718
(95% CI)	*(1.378, 1.496)*	*(0.769, 0.849)*	*(0.672, 0.739)*	*(0.460, 0.511)*	*(2.635, 2.801)*
Concentration–time algorithms to predict AUC	8.88 (6 h) (r^2 = 0.79)	5.35 (6 h) + 3.94 (3.5 h) (r^2 = 0.88)	3.48 (6 h) + 3.07 (3.5 h) + 3.45 (6.5 h) (r^2 = 0.91)	3.27 (6 h) + 2.20 (3.5 h) + 3.53 (6.5 h) + 1.43 (0.5 h) (r^2 = 0.94)	10.35 (12 h) (r^2 = 0.63)
Ziprasidone					
True mean of simulated AUC(0,τ) = 0.90 ± 0.56					
Correlation (r^2)	0.91	0.95	0.97	0.98	0.71
Precision (CV% of AUC)	14.0	8.3	6.6	7.2	41.2
Absolute bias (μg ml^{-1} h^{-1})	0.147	0.090	0.070	0.080	0.428
(95% CI)	*(0.138, 0.155)*	*(0.085, 0.096)*	*(0.066, 0.074)*	*(0.075, 0.085)*	*(0.409, 0.446)*
Concentration–time algorithms to predict AUC	9.91 (6 h)	7.31 (6 h) + 3.75 (0.5 h)	3.98 (6 h) + 3.35 (0.5 h) + 4.09 (6.5 h)	2.19 (6 h) + 3.02 (0.5 h) + 3.24 (6.5 h) + 2.19 (5 h)	11.48 (12 h)

AUC units reported in μg ml^{-1} h. Pearson's correlation used for r^2. Root mean square of the error used as absolute bias estimate. Time in h.

was expected because time point selection is based on minimizing error in all parameters rather than CL alone. The optimal sampling module in ADAPT could be considered an 'individual sampling approach', one that suggests optimal times for a given vector of pharmacokinetic parameter point estimates. In this application of optimal sampling, we used the central/modal population PK parameters to derive suggested sampling times (and then tested performance of these sampling strategies when applied to the full population). Other optimal sampling software packages determine strategies based on the pharmacokinetic parameter likelihood distributions in the population [17, 22, 57–59]. In our experience the two approaches agree well, on minimalistic designs and the population approach has a major advantage when we are able to consider more samples per subject (how best to split several 'late' samples, for example). The two optimal sampling approaches also are more similar when inter-individual variability on CL/*F* is small to moderate and are more likely to differ when inter-individual variability on CL/*F* is large.

The population approach presented here obtained the AUC(0,τ) at steady-state generated on the basis of the three optimal sampling time points for each antipsychotic medicine using a standard two stage MAP-Bayesian population approach, and compared this with the extensive sampling time points based on MCS used to generate the pharmacokinetic parameters. As expected, only minor differences were seen between the two strategies when predicting the AUC in each subject with correlations (r^2) between 0.55 and 1.00 and precision (CV%) between 1.30% and 15.65%. The absolute bias was also reported and gives an indication of the systematic error involved with the algorithms. The correlation between the MAP-driven estimate of risperidone AUC(0,τ) and the true AUC(0,τ) was modest (0.55), and this could be due to the high inter-individual variability in the population, despite only using extensive metabolizers of CYP2D6 in the analysis, but requires further exploration [33]. This demonstrates the advantage of using a Bayesian population approach with prior information, which can use existing data to inform others in the population set, in order to estimate pharmacokinetic parameters in an individual with only sparse data. MAP-Bayesian population approaches have been widely used to individualize dose in a range of therapeutic areas [60–63].

Using MCS and linear regression, a concentration–time algorithm up to four time points was suggested to identify the most important times for predicting AUC. This approach was tailored towards clinicians without access to pharmacometric tools who are interested in investigating dose optimization or TDM strategies. The recommendation of how many time points were required was based on consideration of both the correlation with AUC and the expected error (CV%). This method allows clinicians designing clinical studies for dose optimization to consider sparse sampling strategies and the most important times to collect these samples. Interestingly, this analysis also has implications for TDM which is traditionally conducted by measuring a trough concentration [29, 64]. The correlation with AUC using a single trough concentration for aripirazole, clozapine, olanzapine, perphenazine,

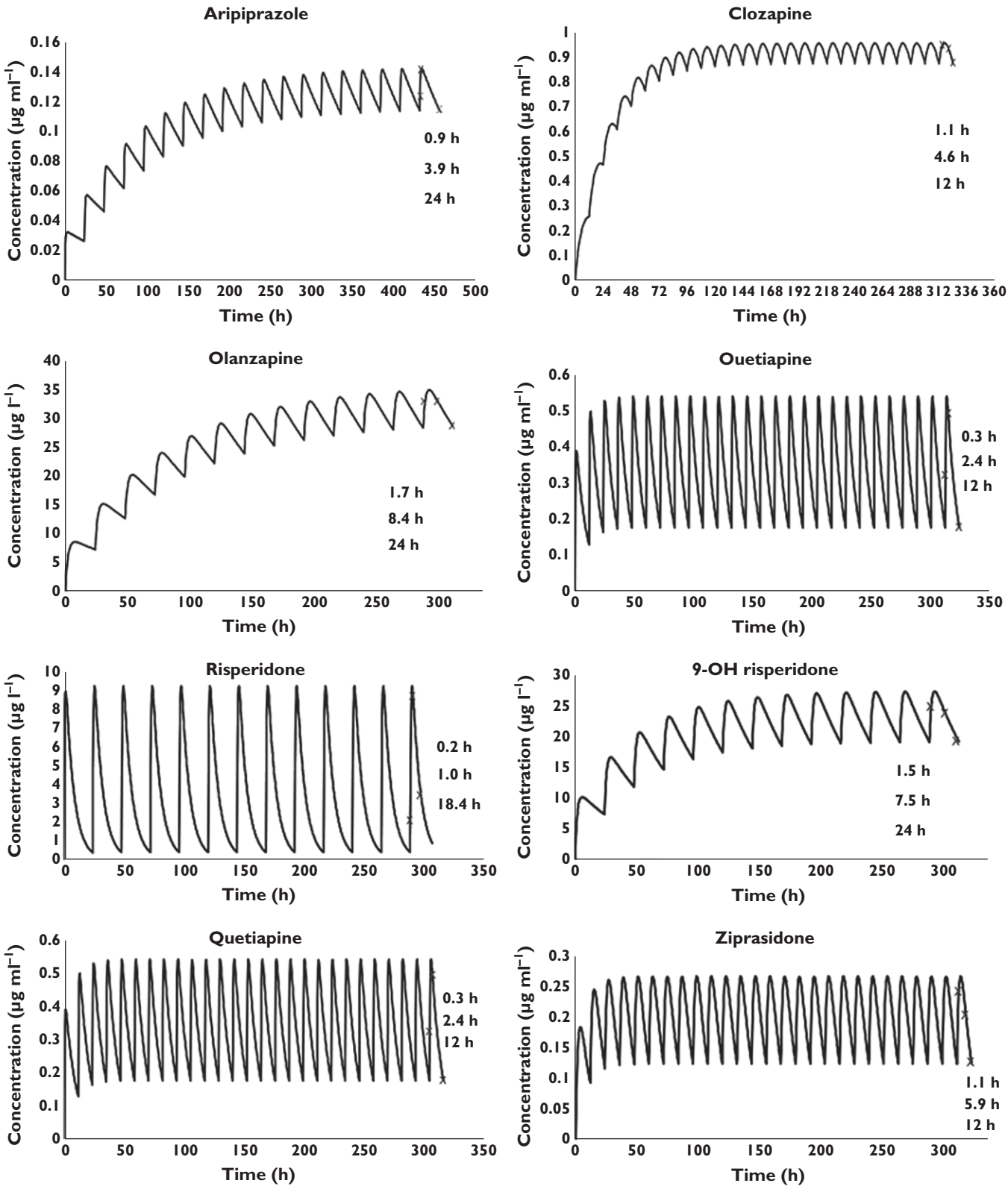

Figure 1

Simulated pharmacokinetic profiles of antipsychotic medicines indicating optimal sampling time points

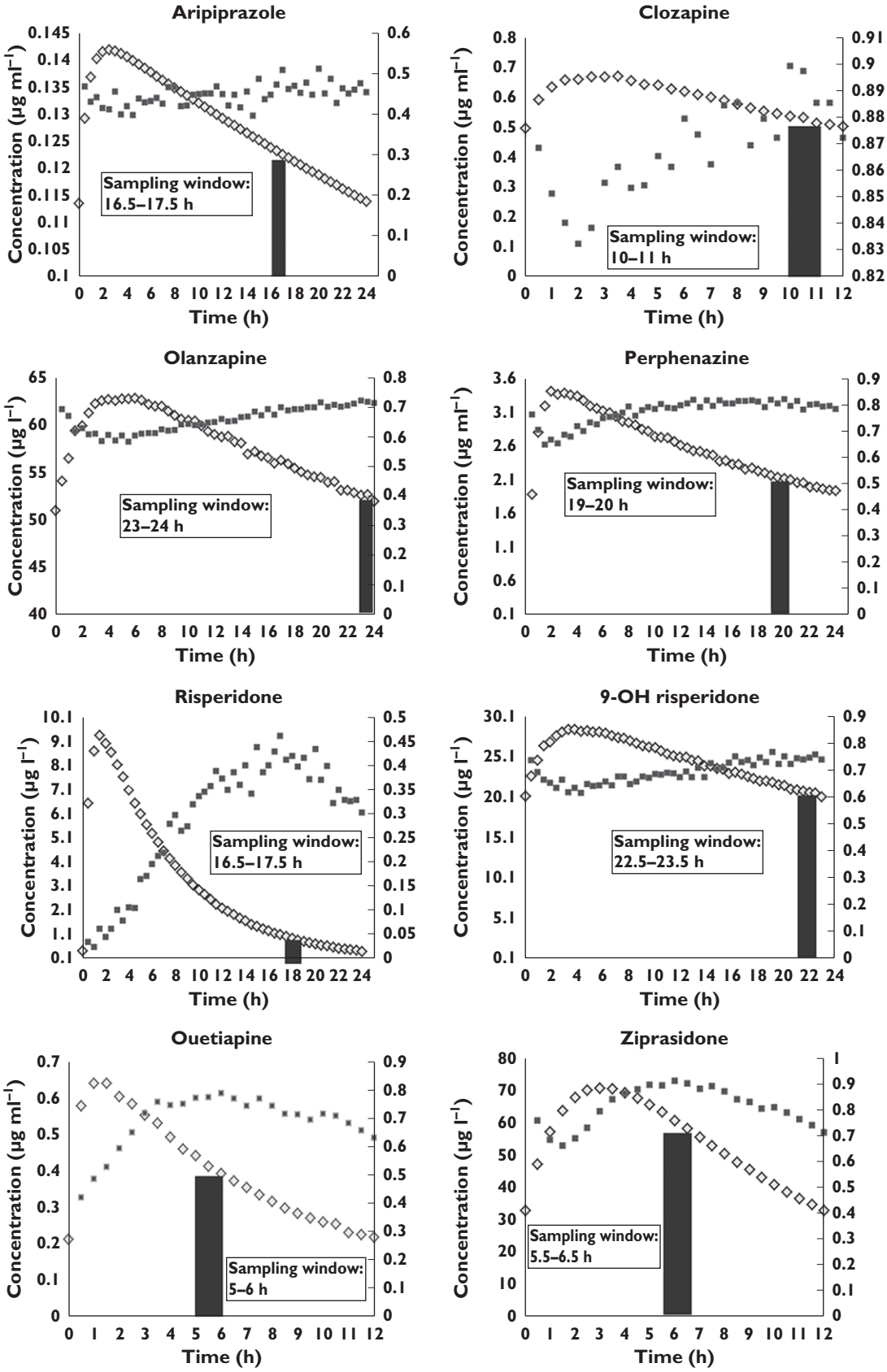

Figure 2

Hourly sampling windows reflecting most appropriate times to capture AUC interval of each antipsychotic medicine. ◇, Concentration (μg ml^{-1}); ■, correlation (r^2)

risperidone, 9-OH risperidone, quetiapine and ziprasidone were 0.67, 0.93, 0.79, 0.77, 0.71, 0.74, 0.63 and 0.71, respectively. The bias in the trough concentration estimate of AUC was also high relative to other specified concentration–time points, indicating that there may be significant deviation from the true value of AUC using these algorithms. Thus, trough concentration shows modest correlations with AUC with high expected error, except in the case of clozapine, which is the only drug with an established therapeutic trough concentration range and is commonly measured in clinical practice. For other antipsychotic drugs including olanzapine, TDM remains controversial with most studies concluding no clear exposure–response relationship [30, 65, 66]. However, if we consider that the trough concentration used in these studies is not an optimal indication of exposure then a relationship to response may not provide a clear reproducible result. Further evaluation is necessary to determine the change in concentration necessary to cause a change in response or toxicity and prospective PK/PD studies may be able to determine this. The calculation of AUC at steady-state, which is a gold standard measure of exposure, is a physiologically plausible correlate or surrogate of response. Previous studies in patients with schizophrenia have indicated that average concentration at steady-state, rather than peak concentrations may be related to average D_2-dopamine receptor occupancy [50]. Enabling clinicians to gather information regarding a standard metric such as AUC allows an easy comparison of adherence, inter-individual and inter-occasional variability which is critical to dose adjustment [67–69].

Typically in clinical settings, patients are available for relatively short consultations and this may only allow for the collection of one blood sample. Therefore, we have suggested the optimal sampling windows (spanning an hour) that give the most accurate calculation of AUC(0,τ). This provides a practical and feasible approach to check adherence and/or potential changes in drug metabolism and disposition on a regular basis. This can be very important considering the constant dose adjustment that is typically observed with antipsychotics.

This study has presented evidence for optimizing sampling times to obtain pharmacokinetic parameters. The optimal sampling times based on D-optimality provide an ideal platform to design future population PK studies, the MCS with an emphasis on identifying single time points serve as a strategic method for future therapeutic drug monitoring strategies in acute hospital situations, with or without the aid of pharmacometric tools, whilst the sampling window identification accounts for the outpatient setting which clinicians may use in order to monitor patients and generate robust measurements of exposure. In the outpatient setting, the sampling windows provide a similar precision for determining individual drug exposure but allow greater flexibility for patient visits given the nature of the typical clinical setting. Furthermore, the sampling windows demonstrate good precision and accuracy to identify individuals at the extreme ends of exposure to these medications and therefore would be highly useful in selecting drug and dose regimens.

There are some limitations that must be considered. Many of the drugs studied here contain active metabolites which contribute to drug efficacy, and therefore future studies which simultaneously model both parent and metabolite will need to be undertaken. Optimal sampling times will be needed for both parent and metabolite to understand their impact on patient response. The CATIE trial, which formed the basis of the optimal sampling times used in this analysis is considered quite 'noisy' data due to the large number of subjects and clinical trial design and thus the expected variability compared with a clinical setting may be over-estimated. The use of optimal sampling analysis to predict the best times to capture the best pharmacokinetic data for a new drug of interest does require knowledge of pharmacometrics. This is an emerging science in clinical settings and expertise in this area may not be available to clinicians.

In conclusion, formalized approaches to guide antipsychotic dosing would be highly valued by clinicians working in mental health. This study identified optimal sampling times for obtaining the pharmacokinetics of antipsychotic medicines in individual patients. This information and approach will enhance clinical trial design and help establish the value of TDM of antipsychotic medicines in psychiatry. The results indicate the potential to increase the accuracy of estimated pharmacokinetic parameters, particularly clearance and AUC, using the suggested optimal sampling strategies. This study provides a guideline for researchers/pharmacometricians and clinicians to undertake PK/PD studies that maximize information that is gained regarding the exposure of patients to a drug. The optimized and sparse sampling makes these studies feasibile and thus minimizes invasiveness, patient discomfort and ultimately costs.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and, with the exception of Dr Bies (see below), declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

Dr Bies reports other from Indiana CTSI through a gift from Eli Lilly and Company, during the conduct of the study; grants from National Institutes of Health, other from Centre for Addiction and Mental Health, University of Toronto, Campbell Family Foundation, non-financial

support from International Society for Pharmacometrics, non-financial support from Metrum Institute, non-financial support from American Association of Pharmaceutical Scientists, Clinical Pharmacology and Translational Research Section, outside the submitted work.

The authors would like to thank Professor Kenneth Williams for his insight into the analysis. Dr Vidya Perera is supported by a postdoctoral fellowship funded by the University at Buffalo/Novartis.

Author contributions

VP: Conceptualized study, conducted the literature search, performed analysis, contributed to the writing of manuscript, responsible for editing for submission.

RRB: Provided insight into CATIE trials, contributed to analytical design and suggestion of extended analysis.

GM: Conducted the literature search, performed analysis, contributed to the writing of manuscript.

MJD: Conducted the literature search, performed analysis, contributed to the writing of manuscript.

VJC: Provided clinical expertise for relevance of results in psychiatry, assisted in design of the study, contributed to the writing of manuscript.

AJM: Contributed to the writing of manuscript, contributed to concept design and aims.

ROD: Provided clinical pharmacology expertise for relevance of results in practice, contributed to the writing of manuscript.

TP: Provided clinical pharmacology expertise for relevance of results in practice, contributed to the writing of manuscript.

AF: Contributed to study design, oversaw conduct of analysis, contributed to the writing of manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1
Methodology describing optimal sampling and assessment of time points for AUC

Figure S2
A diagram of a one compartment pharmacokinetic model

Table S1
Previous studies investigating population pharmacokinetics of antipsychotic medicines